--This application is a continuation of pending Application serial no. 09/454,498 , filed on December 6, 1999, which is a continuing application of 08/946,679 filed October 8, 1997 (issued as U.S. Patent No. 6,087,100); which is a continuing application of 08/709,263 filed September 9, 1996 (issued as U.S. Patent No. 5,780,234); which is a continuing application of 08/166,036 filed December 10, 1993 (issued U.S. Patent No. 5,591,578).--

This statement is found in the transmittal papers filed with this case filed on 5/23/01 with "Express mail label: EL758643422US". The transmittal sheet that the Examiner is referring to belongs to a prior application and is dated Dec. 6, 1999 and is not pertinent to this case.

Rejections under 35 U.S.C.§101: Lack of Utility

Claims 21-32 are rejected under 35 U.S.C.§101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. Applicants respectfully traverse.

The Examiner contends that the specification fails to teach the claimed "nucleotide comprising a covalently attached electron transfer moiety" and thus fails to disclose an asserted specific and substantial utility for the nucleoside. The Examiner also suggests that the synthesis of nucleic acids utilizing such nucleotides comprising bulky adducts like ETMs (electron transfer moiety) are not enabled given the presumption that bulky adducts may hinder enzymatic or chemical synthesis of nucleic acids. Thus, the Examiner concludes that the claims are inoperative and fail to meet the utility requirement under 35 U.S.C. 101. Applicants respectfully disagree.

Applicants assert that the synthesis of nucleic acids utilizing nucleotide triphosphates comprising bulky adducts like ETMs (electron transfer moiety), as taught in the current invention, does not hinder enzymatic or chemical synthesis of nucleic acids.

As a preliminary matter, Applicants assert that the specification provides adequate support for making and using ETM-labeled nucleotides; for example: see page 13, line 5-11, page 20, line 15 through page 21, line 26, page 23 lines 17-23 and all Examples from page 35, line 27 through page 47, line 30. These pages outline both standard solid phase phosphoramidite synthesis as well as enzymatic synthesis, using, for example, using Taq polymerase, T4 DNA polymerase etc. The specification also describes various utilities for nucleic acids with ETMs; for example, see page 10, lines 25-31, which describes use of such nucleic acids as diagnostic probes, or novel bioconductors. Further in support of utility and enablement, Applicants hereby present two articles: (1) A chapter published in a commercially available Handbook by Molecular Probes, namely: "Chemically modified nucleotides, oligonucleotides and nucleic acids": Chapter 8-Section 8.2 in the 'Handbook of Fluorescent probes and Research chemicals' by Richard P. Haugland, 6th edition (attached hereto as Exhibit A); and (2) a research article by Hurley, D. and Tor, Y., *J. Am. Chem. Soc.*, (1998) 120, 2194-5 (attached hereto as Exhibit B). Exhibit A describes fluorophore labeled (bulky adducts; see Fig. 8.4 and Table 8.2) nucleosides and oligonucleotides, that is, Chromatide nucleotides, for enzymatic incorporation into nucleic acids (see page 157, column 1, line 18-21). Furthermore, preliminary experiments were performed to show that the Chromatide nucleotides were functional with a variety of nucleic acid modifying enzymes: viz; Taq polymerase, DNA polymerase, Klenow polymerase, TdT transferase, SP6, T3 and T7 RNA polymerase (see column 1, last paragraph through page 158, first paragraph). Exhibit B describes the synthesis of metal-containing phosphoramidites during solid-phase oligonucleotide synthesis (see Scheme 1and column 1, line 15-21). Thus, there is prior art that teaches the incorporation of bulky adducts during nucleic acid synthesis both using solid-phase standard phosphoramidite chemistry as well as enzymatic synthesis. Since the current specification must be read in view of the existing art, the Examiner's presumption that "incorporation of nucleosides

comprising bulky adducts like ETMs into nucleic acids using enzymatic synthesis or chemical synthesis would not be expected by one of skill in the art" is incorrect.

Since, Applicants have asserted a well established utility for their invention, Applicants respectfully request withdrawal of the rejection of Claims 21-32 under 35 U.S.C. § 101.

Rejections under 35 U.S.C.§112, first paragraph: Lack of Enablement

Claims 21-32 are rejected under 35 U.S.C.§112, first paragraph since the claimed invention is not supported by an asserted utility or an established utility, one of skill in the art would not know how to use the claimed invention. Applicants respectfully traverse.

In view of the discussions above, Applicants have asserted a specific and substantial utility for their invention with adequate support in the specification and in the exhibits attached hereto. Thus, one skilled in the art is fully enabled to make and use this invention.

Accordingly, Applicants respectfully request withdrawal of the rejections to Claims 21-32 under 35 U.S.C. 112, first paragraph for lack of enablement.

Rejections under 35 U.S.C.§112, first paragraph: Lack of Written Description

Claims 21-32 are rejected under 35 U.S.C.§112, first paragraph as containing subject matter which is not described in the specification. Applicants respectfully traverse.

Again, in view of the discussions above, Applicants submit that the specification, as filed, provides a legally sufficient written description for the addition of an electron transfer moiety to a nucleotide and fully complies with the written description requirement. That is, Applicants have fully provided written description of how to make and use ETM-labeled nucleotides in nucleic acids, for example: see page 13, line 5-11, page 20, line 15 through page 21, line 26, page 23 lines 17-23.

Hence, Applicants respectfully request withdrawal of the rejection of claims 21-32 under 35 U.S.C. 112, first paragraph for lack of written description.

Rejections under 35 U.S.C.§112, second paragraph: Indefiniteness

Claims 21-32 are rejected under 35 U.S.C.§112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Specifically, the Examiner contends that the claims are confusing because the function of the "modified nucleotide" and its relationship to the electron transfer moiety are not recited. Applicants respectfully traverse.

Applicants submit that the specification describes addition of transition metal ETMs through a procedure that utilizes modified nucleotides, preferably amino-modified nucleotides (see page 20, line 15-24). Furthermore, the specification clearly describes the method of ETM attachment to an amino-modified nucleotide/ oligonucleotide (see page 37, lines 22, Example 1: step 3), i.e., addition of ruthenium bisbipyridine carbonate (the ETM) to an amino-modified oligonucleotide. Thus the relationship between an ETM and a modified nucleotide is clearly defined.

Thus, Applicants respectfully request that the rejection of claims 21-32 under 35 U.S.C. 112, second paragraph be withdrawn.

Rejections under Provisional type Double Patenting: Obviousness Type

Claims 21-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-25 of copending application no. 09/306,749 and over claims 21-28 of copending application no. 09/602,618.

The Examiner contends that although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a nucleoside comprising a covalently attached ETM.

The Applicants respectfully request that this issue be held in abeyance until otherwise allowable subject matter is found, at which point a terminal disclaimer may be filed.

Conclusion

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 2/13/02

Respectfully submitted,

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